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Resting heart rate as a tool for risk stratification in primary care: does it provide incremental prognostic information?

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Abstract

Background: Several selected population-based studies have emphasized the significance of resting heart rate as an independent cardiovascular risk factor. However, there are no data available for using resting heart rate as a cardiovascular risk predictor in contemporary primary care. Thus, the aim of our analysis was to examine the clinical value of the measurement of resting heart rate in a large, unselected population-based cohort of primary care subjects under the conditions of contemporary primary prevention.
Design: Prospective, population-based cohort study.
Methods: We examined a subgroup of 5320 unselected primary care subjects free of coronary artery disease from the nationwide, longitudinal Diabetes Cardiovascular Risk Evaluation Targets and Essential Data for Commitment of Treatment (DETECT) cohort study, which was conducted from 2003 to 2008.
Results: During the follow-up time of 5 years, 258 events were reported. Elevated resting heart rate was not associated with an increased risk for cardiovascular events (HR=0.75, p=0.394), cardiovascular mortality (HR=0.71, p=0.616) or major cardiovascular events (HR=0.77, p=0.376). By cross-sectional analysis, elevated heart rate clustered with markers of the metabolic syndrome, like increased blood pressure (systolic: OR=5.54, p<0.0001; diastolic: OR=3.82, p<0.0001), elevated fasting plasma glucose levels (OR=8.84, p<0.0001), hypertriglyceridaemia (OR=22.16, p=0.001), and obesity (body mass index OR=0.89, p<0.0001). Assessment of resting heart rate in clinical practice had minimal and non-significant additional prognostic value compared to established cardiovascular risk factors as judged by C statistics (C=0.001, p=0.979).
Conclusion: The measurement of resting heart rate in the daily routine of primary care does not provide incremental prognostic information for cardiovascular risk stratification.

Keywords: Heart rate, metabolic syndrome, primary care, primary prevention, prognostic value, risk stratification

Introduction

Several epidemiological studies have suggested that an elevated heart rate measured at rest might be a predictor of cardiovascular[1,2] and non-cardiovascular mortality.[3,4] Especially the recently published BEAUTIFUL study has re-ignited the interest in the prognostic significance of resting heart rate: although lowering resting heart rate by ivabradine on top of beta-blocker therapy did not have a significant effect on the combined endpoint of cardiovascular morbidity and mortality in patients with coronary artery disease and left-ventricular dysfunction,[5] a sub-group analysis within the placebo arm of the trial showed that a high resting heart rate was a strong independent risk factor for the aforementioned endpoint.[6]

Previous studies in the general population including subjects without known coronary artery disease have produced discrepant findings regarding the significance of resting heart rate as an independent cardiovascular risk factor: analyses of population subgroups such as women,[1] subjects within a narrow age-range[7] or specific occupations, such as industrial workers or civil servants,[4,8] revealed a significant influence of resting heart rate on coronary events and cardiovascular death. However, in the so far largest study,[7] the predictive power of resting heart rate was reduced after adjustment for cardiovascular risk factors. None of the large-scale population-based analyses accounted for primary prevention measures. Thus, it is still unclear whether resting heart rate itself causes higher mortality or whether there is merely an association between resting heart rate and mortality.[9]

Finally, since heart rate is a highly variable biological marker,[10] the question arises as to which extent the results, which were obtained under standardized study conditions, can be extended to primary prevention, and to what degree the predictive value of a resting heart rate measurement in everyday practice is significant for cardiovascular risk stratification.

Therefore, the aim of our analysis was to determine the prognostic significance of resting heart rate as an independent cardiovascular risk factor assessed in a large representative primary care population of individuals free of coronary artery disease under the conditions of contemporary primary prevention. Furthermore, we aimed to assess to which extent a single measurement of heart rate, as measured by general physicians in the context of their everyday work, adds relevant prognostic information for cardiovascular risk stratification in this population of primary care subjects.

Materials and methods

Study population

The Diabetes Cardiovascular Risk Evaluation Targets and Essential Data for Commitment of Treatment (DETECT) – trial is a large multistage prospective longitudinal study. The baseline study consisted of a nationwide representative sample of doctors with primary care functions (medical practitioners, general practitioners, general internists) and included a total of 55,518 unselected consecutive patients recruited on two predefined half-day cut-off dates in 3188 primary care offices in Germany. Subjects were included into the present study during a

routine consultation with the primary physician for a good health examination or for treatment of an acute or chronic non-cardiac disease.

A representative partial sample of 7519 subjects was randomly chosen in 1000 primary care offices and evaluated over a 5-year time period with two assessment points at 12 months and 5 years after inclusion. For inclusion into the present analysis, study participants had to be free of any history of prior myocardial infarction, known coronary artery disease, documented stroke, clinical signs of systolic or diastolic heart failure, and/or chronic kidney disease requiring haemodialysis at baseline.

The DETECT survey received the approval of the Ethics Committee of the Carl Gustav Carus Medical Faculty at the Technical University of Dresden (AZ: EK149092003; 16 September 2003) and registered at clinicaltrials.gov (NCT: 01076608).

Measurements

Details on the methods used in the DETECT study have been described elsewhere.[11] The baseline examination consisted of a standardized medical history, a physical examination, and a laboratory assessment. Subjects additionally completed a self-administered questionnaire, which was used to assess demographic data, smoking history, family history, and information on duration and severity of cardiovascular risk factors and existing medical as well as non-medical treatment. Physicians also completed a questionnaire concerning their patients' symptoms, diagnoses, treatments, and health behaviour. Assessment tools with established reliability and validity were used. Trained staff measured blood pressure according to the guidelines of the German Hypertension League.

Heart rate was measured the way primary care physicians assess this parameter in their daily routine, after an adequate resting period. The same examinations were repeated at the 1-year follow-up.

Endpoints

State of health and medical history during follow up were ascertained at the conclusion of the trial as part of the final assessment in 2008. The following endpoints were documented: all cause mortality, mortality of cardiovascular cause, occurrence of a myocardial infarction, and manifestation of coronary artery disease as evidenced by the necessity for coronary revascularization by either coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). Deaths and known causes of deaths were determined by the treating primary care physicians and supplemented by consulting the national cause of death registry. For analysis, a combined endpoint of 'major cardiovascular events' was used including death from cardiovascular causes, non-fatal myocardial infarction, and necessity for coronary revascularization by CABG surgery or PCI.

Statistical analyses

All participants were subdivided into quartiles based on resting heart rate, as measured by the primary physician. The association of resting heart rate with the different outcomes was investigated with the use of Cox proportional hazards regression. Besides crude analysis, hazard ratios (HRs) were adjusted for confounding variables, which have previously been shown to influence resting heart rate.[12,13] These were age, gender, atrial fibrillation, and rate control medication with beta-blockers or calcium-channel blockers. HRs were additionally

adjusted for established cardiovascular risk factors such as diabetes mellitus, hypertension, smoking status, hyperlipidaemia, and body mass index. In order to evaluate the significance of change in resting heart rate over time, measurements of resting heart rate were performed at the 1-year follow-up and compared to the baseline values. The influence of absolute changes in quartiles of resting heart rate as well as the influence of an increase or decrease of resting heart rate between baseline and the first follow-up time point at 12 months were determined by assessment of HRs.

The association of resting heart rate and the established cardiovascular risk factors was assessed by odds ratios, which were determined by multiple logistic regression analysis. To evaluate the prognostic value of resting heart rate measurement compared to risk stratification using the established cardiovascular risk factors, the C statistic was calculated. The estimates of the C statistic after Cox regression models (with 95% confidence intervals) for conventional cardiovascular risk factors, with and without resting heart rate as a dichotomous variable (heart rate above mean value), were calculated to assess model discrimination. Results are presented as mean ± standard deviation. p-values <0.05 from two-sided test were considered to indicate statistical significance. All statistical analyses were conducted with the use of STATA 11.[14]

Results

Of 7519 patients, 5320 patients with a complete data set and without known coronary artery disease (CAD) were included in the final analysis. Their baseline characteristics are shown in Table 1. The majority of participants was female, the mean age was 55.9 ± 13.7 years and 1852 participants (34.8%) had arterial hypertension. Antihypertensive treatment consisted of angiotensin-converting enzyme inhibitors/angiotensin receptor blocker (26%), beta-blockers (20.4%), calcium- channel blockers (10.3%), or diuretics (12.8%). For hyperlipidaemia, 10.9% were treated with a statin, and 3.5% of participants suffered from insulin-dependent diabetes mellitus. The average resting heart rate was 72.8±9.9 beats per minute (bpm) at inclusion into the study and 72.3 bpm ± 9.8 at the follow-up examination after 1 year. Within the study cohort, the mean estimated 10-year risk for a serious cardiovascular event calculated by the Framingham risk score was 13.8% ± 5.3. The main reason for seeing a primary care physician was for a check-up examination.

During the follow-up time of 5 years, a total number of 258 incident events (4.85%) was observed: There were 137 (2.58%) deaths in total; of these, 22 (0.41%) deaths were of cardiac-related cause (myocardial infarction, sudden cardiac death). In 121 (2.27%) subjects, a cardiovascular event (non-fatal myocardial infarction, revascularization by CABG or PCI) occurred.

Figure 1 shows the relative risk of the study cohort for the endpoints all-cause mortality, cardiovascular mortality, occurrence of a serious cardiovascular event (non-fatal myocardial infarction or revascularization by CABG or PCI), and major cardiovascular event (myocardial infarction, revascularization by CABG or PCI, or death from cardiovascular cause) within the 5-year follow-up period. There was no significantly increased risk as expressed by HRs in higher quartiles of heart rate compared to the lowest quartile of heart rate, except for all-cause mortality of women, which was significantly higher (HR=2.99; p=0.011, crude) in the subgroup of women within the highest quartile of resting heart rate.

After adjustment for cofactors that influence heart rate (age, gender, atrial fibrillation, and rate control medication) and further adjustment for established cardiovascular risk factors (hypertension, diabetes mellitus, smoking status, family history, hyperlipidaemia and body mass index), no detectable influence of resting heart rate on any of the study endpoints was observed (Table 2).

While classical, established cardiovascular risk factors, such as arterial hypertension (HR=4.80; p<0.0001), hyperlipidaemia (HR=2.16; p<0.0001), and diabetes mellitus (HR=2.87; p<0.0001), demonstrated significantly increased HRs within the study cohort, neither a cut-off value of 70 bpm nor a study specific cut-off of mean heart rate (72.8 bpm) was associated with an increase of risk for major cardiovascular events in a crude statistical model or after adjustment for age and gender (Table 3).

Since a one-time measurement of resting heart rate in primary care did not show an association with the various endpoints in the 5-year follow-up period, the relative risk of repeated heart rate measurements was determined. To assess the prognostic value of a repeated measurement of resting heart rate, we used the data obtained at the first follow-up after 1 year (2004) (n=4472). We determined the absolute change of resting heart rate as well as an increase or decrease of heart rate, and calculated the relative risk of changes in heart rate during repeated measurements for onset of major cardiovascular events during follow-up. As shown in Table 4, there was no significant influence on relative risk for the combined endpoint of a major cardiovascular event within the remaining follow-up period of 4 years. Even for a potentially high-risk cohort of primary care subjects, who had repeatedly elevated resting heart rate in the highest quartile, we could not observe an increase of risk (HR=1.09; p=0.862 crude) for a major cardiovascular event.

In order to characterize patients within the quartiles of heart rate, we performed a cross-sectional analysis between heart rate quartiles and established cardiovascular risk factors (Table 5). The prevalence of cardiovascular risk factors, such as smoking (OR=1.54; p<0.0001), hypertriglyceridaemia (OR=22.16; p= 0.001), and diabetes mellitus (OR=1.70; p<0.0001) was significantly higher in subjects within the highest quartile of heart rate compared to the lowest quartile of heart rate. Likewise, the mean systolic and diastolic blood pressure value as well as obesity increased significantly with increasing quartiles of resting heart rate.

To finally evaluate the significance of a single measurement of resting heart rate in primary care compared to risk stratification by established cardiovascular risk factors, we determined the additive predictive value of resting heart rate by C statistic for Cox regression models. As shown in Table 6, the additional measurement of heart rate had no additional effect on risk stratification compared to a model based only on established cardiovascular risk factors, including age, gender, systolic and diastolic blood pressure, hyperlipidaemia, diabetes mellitus, obesity, smoking status, and family history of coronary artery disease (C=0.803; p=0.979).

Discussion

In a representative cohort of primary care subjects without existing coronary artery disease (CAD) at baseline, studied under the conditions of contemporary primary prevention, the one-time measurement of resting heart rate in the primary physicians' office did not provide prognostic information on cardiovascular outcome over and above classical risk factors for

CAD. Resting heart rate in this setting was not an independent cardiovascular risk factor for different endpoints of mortality and cardiovascular morbidity, but was associated with established cardiovascular risk.

Significance of resting heart rate as a risk factor in primary prevention

A multitude of recent studies emphasized the potential significance of resting heart rate as an independent cardiovascular risk factor. While the influence of resting heart rate on the progression of existing cardiac disease has been highlighted impressively in several epidemiological analyses[15,16] and clinical trials,[6,17] the data available for resting heart rate as a cardiovascular risk factor in subjects free of coronary artery disease is inconclusive. In one of the largest analysis so far in nearly 380,000 subjects, all within one age-group of 40–45 years, the predictive power of resting heart rate for cardiovascular mortality was lost after adjustment for other cardiovascular risk factors.[7] In contrast, a large trial including only postmenopausal women free of cardiovascular disease emphasized the role of heart rate as an independent predictor of cardiovascular death and non-fatal myocardial infarction.[1] Nauman et al.[18] reported a strong association between resting heart rate and cardiovascular mortality in a study cohort of about 50,000 patients followed-up for over 18 years. However, the study was initiated in the early 1980s, a time when cardiovascular primary prevention strategies did not yet include angiotensin-converting enzyme inhibitors or statin therapy, which were shown to play an important role in reducing cardiovascular mortality in primary prevention.[19–21] Moreover, a significant change of the cardiovascular risk profile is seen over the past two decades.[22] In the present study, the mean body mass index was 2 kg/m2 higher and there was a higher proportion of other cardiovascular risk factors compared to the study by Nauman et al.[18]

Elevated heart rate is well established to cluster with measures of the metabolic syndrome, e.g. obesity, increased diastolic and systolic blood pressures, dyslipidaemia, and elevated insulin and glucose levels. Indeed, the present study confirmed the significant correlation between different clusters of the insulin resistance syndrome and resting heart rate, thus further supporting previous findings that the metabolic syndrome is characterized by sympathetic overdrive and that this condition is mirrored by an increase in heart rate.[23–25] Finally, cardiac autonomic neuropathy, as a long-term consequence of metabolic dysregulation and diabetic metabolism, provides another mechanistic link of elevated heart rate and the metabolic syndrome.[26] Taken together, the data derived from the present study suggest that increased heart rate rather appears to be a ‘risk marker’ correlating with features of the metabolic syndrome than an independent cardiovascular ‘risk factor’ in a contemporary primary prevention cohort.

Prognostic information of the measurement of resting heart rate in primary care

Contrary to previous studies, an important goal of our study was not only to investigate the association between resting heart rate and different endpoints, but rather to test the practical implications of measuring resting heart rate by primary physicians the way it is assessed in their daily routine.

The clinical value of a marker should be assessed by its effect on patient management and outcome and by the degree of incremental prognostic information it provides.[27] All existing studies that have emphasized the importance and prognostic significance of resting heart rate

are based on heart rate measurements under standardized conditions, which took into account well-known confounders of heart rate assessment.[10,28]

In our analysis, the measurement of resting heart rate was performed as realistically as possible in the setting of primary physicians' offices, and in this setting no additive predictive value of resting heart rate on top of established cardiovascular risk factors could be identified. This finding leads us to question the conclusion of other studies that emphasize resting heart rate as an independent risk factor, as it is difficult for primary care physicians to validly assess resting heart rate within their daily routine and without the possibility of reproducing standardized conditions for heart rate measurement. This is emphasized by our findings that repetitive measurements of heart rate by the same primary physician do not lead to improved risk stratification over a one-time measurement.

Limitations

Some limitations of our analysis merit discussion. First, follow-up time was 5 years in the present study, whereas previous community-based studies reported on follow-up times ranging up to 18 years.[18] Given the rapid developments in pharmacological therapies emerging in primary prevention over the last decade, we felt it to be important to limit the follow-up observation period in order to avoid potential confounding effects of changing clinical practice in primary prevention strategies, e.g. the emergence of statin or angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy being used across a broad range of cardiovascular risk since the late 1990s and early 2000s. Second, according to a recent recommendation, we restricted our combined endpoint to the occurrence of myocardial infarction, coronary revascularization by PCI or CABG and cardiovascular mortality due to sudden cardiac death or fatal myocardial infarction. We do believe that this is an appropriate choice given that this combined endpoint has not only been used in previous risk-stratifying models, but is also a universally accepted endpoint used in major cardiovascular clinical trials evaluating pharmacological interventions for primary prevention.[29]

Finally, the rather moderate number of events during 5 years of follow-up may have limited the statistical power of our analysis. While power calculations using the sample size and event rates of the present study revealed that the conclusions drawn appear to be statistically solid for the male study population, there remain some uncertainties regarding the female study cohort. Indeed, the association between allcause mortality and resting heart rate was of borderline statistical significance ($p=0.055$) in the female cohort. Thus, the rather moderate number of deaths in the female study cohort may have obscured a significant association. In addition, previous studies have demonstrated a weak, albeit statistically significant association between all-cause mortality and resting heart rate in female subjects.[14,30] Taken together, we cannot fully exclude that assessing resting heart rate might be useful in female primary care subjects, and it might be worthwhile to examine potential gender differences in the utility of resting heart rate to predict prognosis.

Conclusions

We conclude that the measurement of heart rate in the daily routine of primary care does not provide relevant prognostic information for cardiovascular outcome. However, we detected an association between increased heart rate and parameters of the metabolic syndrome.

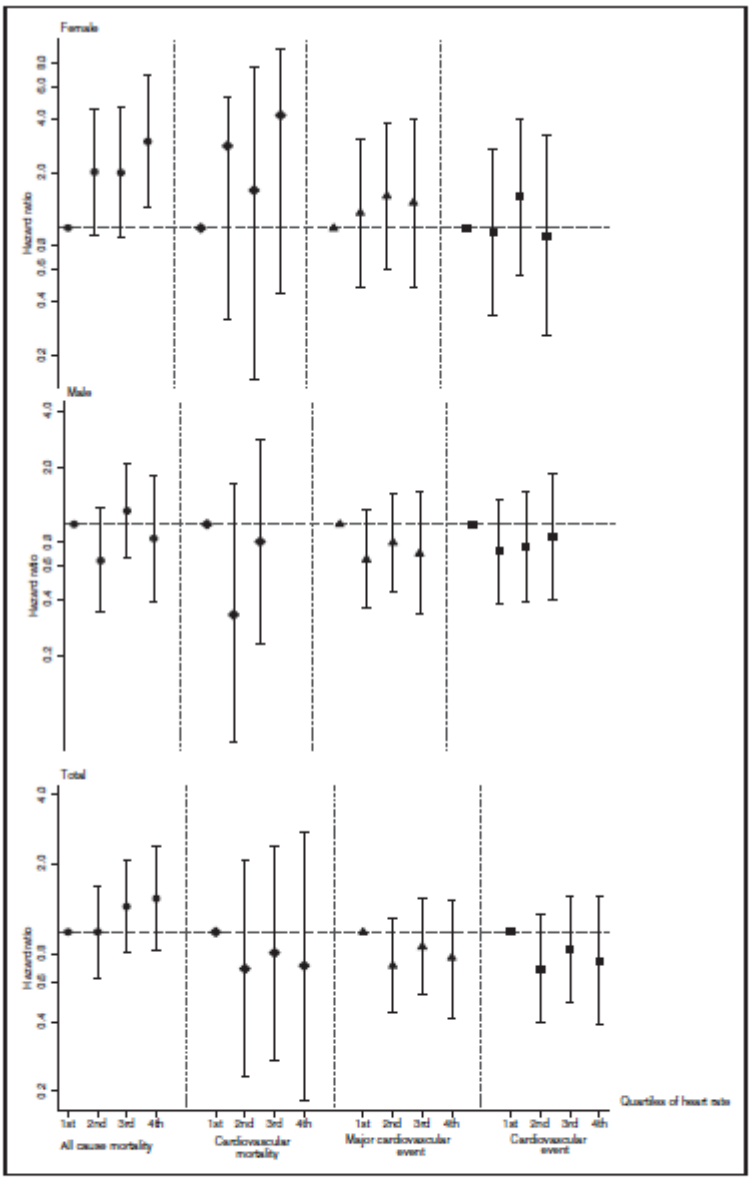

Figure 1. Relative risk of follow-up events by resting heart rate quartiles in the entire study population ($n = 5320$). The figure shows the relative risk (crude) of the follow-up events all-cause mortality, cardiovascular mortality, major cardiovascular event, and cardiovascular event by quartiles of resting heart rate, as demonstrated by bar graphs showing mean values as well as the standard deviation. Hazard ratios (HRs) are shown for the entire study population (bottom graph), as well as stratified by gender. There was no significantly increased risk as expressed by HRs in higher quartiles of heart rate compared to the lowest quartile of heart rate, except for all-cause mortality of women, which was significantly higher (HR = 2.99; $p = 0.011$) in the subgroup of women within the highest quartile of resting heart rate.

Table 1. Baseline characteristics of the study population ($n = 5320$)

Characteristic	Population
Age (years)	55.9 ± 13.7
Female	3301 (62.1)
Heart rate at baseline (bpm)	72.8 ± 9.9
Heart rate at 1-year follow-up (bpm)	72.3 ± 9.8
Hypertension	1852 (34.8)
Systolic blood pressure (mmHg)	131.7 ± 18.2
Diastolic blood pressure (mmHg)	80.1 ± 9.8
Antihypertensive treatment	1631 (32.2)
Angiotensin-converting enzyme inhibitor	843 (16.6)
Beta-blocker	1035 (20.4)
Calcium-channel blocker	521 (10.3)
AT1 receptor antagonist	479 (9.4)
Diuretics	648 (12.8)
Diabetes mellitus	659 (12.4)
Insulin treatment	179 (3.5)
Hyperlipidaemia	1493 (28.1)
Statins	554 (10.9)
Other lipid-lowering drugs	148 (2.9)
Total cholesterol (mg/dl)	225.6 ± 42.0
HDL cholesterol (mg/dl)	55.7 ± 18.5
LDL cholesterol (mg/dl)	129.2 ± 33.2
Smoking	
Current smoker	1034 (21.1)
Ex-smoker	1207 (24.6)
Renal failure	275 (5.2)
Creatinine (mg/dl)	1.2 ± 0.2
Family history of CAD	775 (15.0)
Obesity	
Hip-to-waist ratio	1.13 ± 0.13
Body mass index (kg/m^2)	26.9 ± 4.8

Values are number of subjects with existing data (%) or mean ± standard deviation. bpm, beats per minute; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2. Relative risk of follow-up events by resting heart rate quartiles in the entire study population in statistically adjusted models ($n = 5320$)

	1st quartile (35–66 bpm) $n = 1349$ (25.4%)	2nd quartile (67–72 bpm) $n = 1678$ (31.5%)			3rd quartile (73–80 bpm) $n = 1430$ (26.9%)			4th quartile (81–120 bpm) $n = 863$ (16.2%)		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Adjusted for age, gender, atrial fibrillation, and rate control medication										
All-cause mortality	–	1.05	0.66–1.68	0.823	1.43	0.91–2.27	0.122	1.66	0.98–2.82	0.058
Cardiovascular mortality	–	0.81	0.28–2.28	0.684	0.96	0.33–2.77	0.943	0.96	0.25–3.65	0.953
Major cardiovascular events	–	0.86	0.53–1.41	0.554	1.11	0.69–1.79	0.674	1.06	0.59–1.91	0.850
Cardiovascular events	–	0.85	0.49–1.48	0.571	1.10	0.65–1.88	0.720	1.04	0.54–2.00	0.903
Adjusted for age, gender, atrial fibrillation, rate control medication, diabetes mellitus, hypertension, smoking status, family history of CAD, hyperlipidaemia, and body mass index										
All-cause mortality	–	1.11	0.66–1.86	0.703	1.44	0.85–2.44	0.177	1.58	0.86–2.92	0.140
Cardiovascular mortality	–	0.36	0.11–1.22	0.101	0.47	0.14–1.60	0.225	0.84	0.22–3.31	0.808
Major cardiovascular events	–	0.69	0.41–1.18	0.179	1.01	0.61–1.67	0.984	0.93	0.49–1.75	0.816
Cardiovascular events	–	0.78	0.43–1.40	0.402	1.12	0.63–1.96	0.705	0.94	0.46–1.90	0.859

bpm, beats per minute; CAD, coronary artery disease; HR, hazard ratio estimated by Cox regression model; 95% CI, 95% confidence interval.

Table 3. Relative risk of major cardiovascular events by different cardiovascular risk factors at baseline ($n = 5320$)

	HR	95% CI	*p*-value
Crude			
Heart rate above 70 bpm	0.84	0.58–1.22	0.365
Heart rate above mean value[a]	0.98	0.67–1.43	0.923
Hypertension	4.80	3.17–7.27	<0.0001
Hyperlipidaemia	2.16	1.48–3.13	<0.0001
Diabetes	2.87	1.91–4.33	<0.0001
Obesity	1.71	1.16–2.53	0.007
Adjusted for age and gender			
Heart rate above 70	0.97	0.67–1.42	0.886
Heart rate above mean value[a]	1.11	0.76–1.62	0.585
Hypertension	2.87	1.87–4.41	<0.0001
Hyperlipidaemia	1.61	1.11–2.35	0.012
Diabetes	1.73	1.14–2.61	0.009
Obesity	1.52	1.02–2.25	0.037

bpm, beats per minute; HR, hazard ratio estimated by Cox regression model; 95% CI, 95% confidence interval. [a]Mean value = 72.8 bpm.

Table 4. Relative risk of major cardiovascular events with onset between first and second follow-up by the change in heart rate between baseline and first follow-up ($n = 4472$)

Δ Heart rate baseline to first follow-up	HR[a]	95% CI	*p*-value	HR[b]	95% CI	*p*-value	HR[c]	95% CI	*p*-value
Stable	Reference			Reference			Reference		
Absolute change of 1 quartile	1.24	0.78–1.97	0.368	1.25	0.78–2.00	0.351	1.44	0.88–2.36	0.148
Absolute change of 2 quartiles	1.12	0.60–2.08	0.718	1.10	0.60–2.02	0.758	0.97	0.47–1.99	0.929
Absolute change of 3 quartiles	0.34	0.05–2.51	0.291	0.29	0.04–2.13	0.224	0.32	0.04–2.36	0.261
4th quartile at baseline and follow-up	1.09	0.42–2.81	0.862	1.39	0.54–3.61	0.497	1.43	0.54–3.83	0.471
Decrease of 3 quartiles	–	–	–	–	–	–	–	–	–
Decrease of 2 quartiles	1.45	0.72–2.93	0.299	1.37	0.70–2.67	0.354	1.24	0.55–2.82	0.602
Decrease of 1 quartile	1.15	0.67–1.98	0.604	1.13	0.65–1.95	0.671	1.16	0.64–2.10	0.633
Stable	Reference			Reference			Reference		
Increase of 1 quartile	1.29	0.77–2.19	0.336	1.28	0.75–2.16	0.364	1.59	0.93–2.70	0.087
Increase of 2 quartiles	0.75	0.29–1.92	0.552	0.72	0.28–1.85	0.500	0.57	0.17–1.88	0.359
Increase of 3 quartiles	0.78	0.11–5.74	0.807	0.48	0.07–3.53	0.472	0.57	0.07–4.30	0.581

HR, hazard ratio estimated by Cox regression model; 95% CI, 95% confidence interval. [a]Unadjusted HR. [b]HR adjusted for age, gender, atrial fibrillation, and rate control medication. [c]HR adjusted for age, gender, atrial fibrillation, rate control medication, diabetes mellitus, hypertension, smoking status, family history for coronary artery disease, hyperlipidaemia, and body mass index.

Table 5. Cross-sectional association of heart rate and established cardiovascular risk factors for the entire study cohort ($n = 5320$)

	1st quartile (35–66 bpm)	2nd quartile (67–72 bpm)		3rd quartile (73–80 bpm)		4th quartile (81–120 bpm)	
	$n = 1349$ (25.4%)	$n = 1678$ (31.5%)		$n = 1430$ (26.9%)		$n = 863$ (16.2%)	
Factor	Mean ± SD or % (reference)	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Obesity							
Body mass index (kg/m^2)	26.5 ± 4.4	0.33 (0.00–0.66)	0.050	0.57 (0.22–0.93)	0.002	0.89 (0.48–1.30)	<0.0001
Waist circumference, male (cm)	99.4 ± 11.5	1.47 (0.08–2.87)	0.038	2.57 (1.10–4.04)	0.001	4.58 (2.83–6.34)	<0.0001
Waist circumference, female (cm)	88.3 ± 13.7	1.02 (−0.32–2.35)	0.135	1.38 (−0.02–2.79)	0.054	2.85 (1.32–4.38)	<0.0001
Hypertension							
Diastolic blood pressure (mmHg)	78.7 ± 9.9	0.76 (0.07–1.46)	0.031	1.98 (1.27–2.70)	<0.0001	3.82 (2.92–4.72)	<0.0001
Systolic blood pressure (mmHg)	129.8 ± 18.5	1.24 (−0.05–2.52)	0.060	2.32 (0.96–3.67)	0.001	5.54 (3.91–7.18)	<0.0001
Cholesterol							
Total cholesterol (mg/dl)	223.3 ± 42.4	3.15 (0.17–6.13)	0.038	3.27 (0.11–6.42)	0.043	2.50 (−1.26–6.27)	0.193
HDL cholesterol (mg/dl)	55.5 ± 18.4	0.44 (−0.89–1.77)	0.517	0.55 (−0.83–1.93)	0.437	−0.87 (−2.48–0.73)	0.285
Triglyceride (mg/dl)	143.6 ± 122.2	3.65 (−4.86–12.17)	0.400	8.02 (−0.78–16.83)	0.074	22.16 (8.58–35.75)	0.001
Diabetes							
Diabetes mellitus	9.9	1.29 (1.03–1.62)	0.030	1.31 (1.03–1.66)	0.028	1.70 (1.31–2.19)	<0.0001
Fasting plasma glucose (mg/dl)	95.7 ± 26.3	3.85 (1.67–6.02)	0.001	5.07 (2.82–7.32)	<0.0001	8.84 (5.88–11.80)	<0.0001
HbA Ic (%Hb)	5.4 ± 0.7	0.07 (0.02–0.13)	0.005	0.07 (0.02–0.13)	0.008	0.13 (0.06–0.20)	<0.0001
Smoking							
Current smoker	18.0	1.12 (0.93–1.36)	0.235	1.36 (1.12–1.65)	0.002	1.54 (1.24–1.91)	<0.0001
Treatment							
Anti-hypertensive agents[a]	96.5	0.60 (0.33–1.12)	0.110	0.54 (0.29–1.00)	0.052	0.39 (0.20–0.74)	0.004
Anti-diabetic agents[a]	68.7	1.44 (0.88–2.36)	0.144	1.06 (0.65–1.74)	0.809	1.35 (0.79–2.32)	0.273
Lipid-lowering treatment[a]	49.3	0.93 (0.68–1.27)	0.656	0.83 (0.60–1.13)	0.239	0.87 (0.60–1.26)	0.471

[a]Treatment in case of presence of the respective disease. bpm = beats per minute; HDL, high-density lipoprotein; OR, odds ratio.

Table 6. Additive predictive value of heart rate for predicting future major cardiovascular events ($n = 5320$)

	Major cardiovascular event	
	C statistics	*p*-value
Established risk factors[a]	0.802	
Established risk factors + heart rate >73 bpm	0.803	0.979
Estimated difference	0.001	0.979

[a]Age, gender, systolic blood pressure, diastolic blood pressure, smoking status, family history of coronary artery disease, hyperlipidaemia, diabetes mellitus, and obesity. bpm, beats per minute.

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Conflict of interest

None of the authors have any conflict of interest pertaining to the data presented or have published or submitted any related papers from the same study.

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